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ORIGINAL RESEARCH ARTICLE

Safety and Efficacy of Colchicine in Patients with Stable CAD and ACS: A Systematic Review and Meta-analysis

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Abstract

Background Evidence from recent trials has shown conflicting results in terms of the utility of colchicine in patients with coronary artery disease (CAD).

Methods Multiple databases were queried to identify all randomized controlled trials (RCTs) comparing the merits of colchicine in patients with acute coronary syndrome (ACS) or stable CAD. The pooled relative risk ratio (RR) of major adverse cardiovascular events (MACE), its components, and gastrointestinal (GI) adverse events were computed using a random-effect model.

Results Ten RCTs comprising a total of 12,761 patients were identified. At a median follow-up of 12 months, there was a significantly lower risk of MACE [RR 0.66, 95% confidence interval (CI) 0.45–96], ACS (RR 0.66, 95% CI 0.45–0.96), ischemic stroke (RR 0.42, 95% CI 0.22–0.81), and need for revascularization (RR 0.61, 95% CI 0.42–90) in patients receiving colchicine compared with placebo. A subgroup analysis based on the clinical presentation showed that the significantly lower incidence of MACE and stroke were driven by the patients presenting with ACS. The use of colchicine in patients with stable CAD did not reduce the incidence of MACE (RR 0.55, 95% CI 0.28–1.09), ACS (RR 0.52, 95% CI 0.25–1.08), or stroke (RR 0.61, 95% CI 0.33–1.13). There was no significant difference in the relative risk of cardiac arrest, ACS, cardiovascular mortality, and all-cause mortality between the two groups in both ACS and stable CAD populations. The risk of GI adverse events was significantly higher in patients receiving colchicine (RR 2.10, 95% CI 1.12–3.95).

Conclusion In patients presenting with ACS, low-dose colchicine might reduce the incidence of MACE, stroke, and the need for revascularization at long follow-up durations. Colchicine might offer no benefits in reducing the risk of ischemic events in patients with stable angina.

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Key Points

This systematic review and meta-analysis was conducted to define the role of colchicine in patients with coronary artery disease.

Low-dose colchicine appeared to reduce the incidence of major adverse cardiovascular events, stroke, and the need for revascularization in patients with acute coronary syndromes.

Colchicine did not appear to exert any benefit in patients with stable coronary artery disease.

1 Introduction

Inflammation plays a pivotal role in the initiation, progression, and complications of coronary artery disease (CAD) [1–3]. The landmark Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) showed a significant reduction in cardiovascular events in patients with acute coronary syndrome (ACS) through targeted inhibition of interleukin (IL)-1β [4]. However, these clinical benefits were not reproduced in the Cardiovascular Inflammation Reduction Trial (CIRT), which used low-dose methotrexate as secondary prevention therapy in patients with chronic coronary disease [5]. Methotrexate did not reduce levels of the inflammatory markers (IL-1β) and, hence, was not associated with lower cardiovascular adverse events. On the contrary, by preventing neutrophil-mediated fissuring and rupture of atheroma, colchicine can potentially reduce the incidence of ACS in patients with stable CAD and recent ACS [6]. Colchicine is known to exert its anti-inflammatory effects through a variety of complex mechanisms that ultimately lead to inhibition of innate immunity by downregulating tubulin polymerization and negative modulation of downstream inflammatory cascades [7]. In de novo ACS, the anti-proliferative properties of colchicine could conceivably interfere with neo-intimation and in-stent restenosis, potentially reducing the risk of cardiovascular events [8]. These theoretical benefits have led researchers to investigate the utilization of colchicine in patients with stable CAD and ACS.

The earlier study of the Colchicine Cardiovascular Outcomes Trial (COLCOT), involving patients who had a recent myocardial infarction (MI), showed a lower risk of the primary composite endpoint among patients receiving colchicine compared to those in the placebo arm [9]. These findings were mostly driven by a lower rate of stroke and urgent hospitalizations for angina leading to revascularization. More recently, the Colchicine in Patients with acute coronary Syndromes (COPS) trial demonstrated no cardiovascular benefits and higher mortality associated with the use of colchicine [10]. By contrast, colchicine use in patients with chronic coronary disease remained beneficial in the Low Dose Colchicine (LoDoCo) trials [11, 12]. Overall, due to the conflicting results of the trials, varying patient populations, different clinical outcomes, and methodological limitations, these studies have only added to the growing uncertainty about the practical use of colchicine. Our study aims to bring consensus on the clinical use of colchicine in patients with stable CAD and ACS.

2 Methods

2.1 Search Strategy

The present meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Handbook for Interventional Reviews. A structured comprehensive literature search of digital databases, including PubMed, Ovid, Embase, and Cochrane, up to April 2020 was carried out. A combination of keywords and medical subject headings (MeSH) for "colchicine" was combined with a list of MeSH terms for CAD, including; "CAD," "ischemic heart disease," "stable angina," "coronary artery disease," "myocardial infarction," "MI," and "STEMI" (ST-elevation myocardial infarction). The results from all possible combinations were combined and screened for relevance. Based on our selection criteria, studies from the reference lists related to our clinical question were also screened by an independent author (backward snowballing). The detailed search strategy is given in the electronic supplementary material.

2.2 Selection Criteria and Outcomes

All randomized controlled trials (RCTs) enrolling patients age > 18 years and studying the utility of colchicine in patients with ACS or stable CAD were included. At least one clinical outcome and a minimum follow-up duration of 1 month were used as a cut-off for RCTs to be included in the analysis. Observational studies, studies with non-CAD patients or duplicate data, case series, case reports, and review articles were excluded. The primary efficacy outcome was adjusted major adverse cardiovascular events (MACE), a composite of cardiovascular mortality, non-fatal MI, and non-fatal ischemic stroke. The pooled estimate of trial-defined composite endpoints was also obtained. Secondary efficacy endpoints included the need for revascularization, cardiac arrest, cardiovascular mortality, and individual components of MACE. The definition of stroke varied between the studies; the COLCOT reported both ischemic and hemorrhagic strokes, while the LoDoCo-2 trial only reported ischemic strokes. For this study, we have included only ischemic stroke events in our analysis. The major safety endpoint was the pooled estimate of all gastrointestinal (GI) adverse events.

2.3 Statistical Analysis

The statistical analysis was performed using the DerSimonian and Laird method under the random-effects model to

calculate the risk ratio (RR) for safety and efficacy endpoints. To assess the impact of potential covariates on pooled effect size, an adjusted RR of net results was calculated, based on the standard definition of MACE and equated doses of colchicine. Sensitivity analysis based on the "leave-one-out" method was performed to determine the influence of individual studies on pooled estimates and to assess heterogeneity in the outcomes of the included studies. To avoid the influence of varying selection criteria, a subgroup analysis stratified on the basis of presentation (stable CAD vs. ACS) and follow-up duration was also performed. The Higgins *I*-squared (I^2) statistic model was used to evaluate heterogeneity in the included studies. I^2 values of 50% or less corresponded to low to moderate, and 75% or higher indicated large amounts of heterogeneity. The methodological quality analysis was performed using the risk-of-bias tool version 2 (RoB 2) and the Oxford quality scoring system with Jadad scale. In the former, all included RCTs were screened for five different types of bias (selection, performance, detection, attrition, and reporting bias). All estimated effect sizes were reported as a point estimate with its 95% confidence interval (CI). An alpha criterion of a p value less than 0.05 was considered statistically significant. The publication bias was illustrated graphically with funnel plotting. All statistical analysis was performed using STATA version 16.

3 Results

Our extensive literature search revealed 2312 items. After the removal of 1101 irrelevant and 1132 duplicate items, 79 articles were deemed relevant for full-text review. A total of 69 articles were excluded based on our inclusion criteria; ten RCTs qualified for final quantitative analysis. All included RCTs enrolled patients with stable CAD or ACS. The PRISMA flow diagram detailing study selection is shown in Fig. 1.

A total of 12,761 patients (6428 in the colchicine group and 6333 in the control group) were included. The mean age of the population was 61 years, and 81% were male patients. Of the total population, 37%, 47%, and 60% had a history of smoking, hypertension, and hyperlipidemia, respectively. The proportions of baseline comorbidities were mostly similar between the two groups across most of the included studies, with few exceptions. Deftereos et al. [8] included only diabetes mellitus (DM) patients, while the mean proportion of DM patients in the remaining studies was about 18%. About 51% of the population in the COOL trial had a positive family history of CAD. There was significant heterogeneity in the selection criteria, patient population, and follow-up durations of the included studies ($I^2 = 53\%$ for MACE). The COLCOT included patients within 30 days of an index ACS event, while both LoDoCo and LoDoCo-2

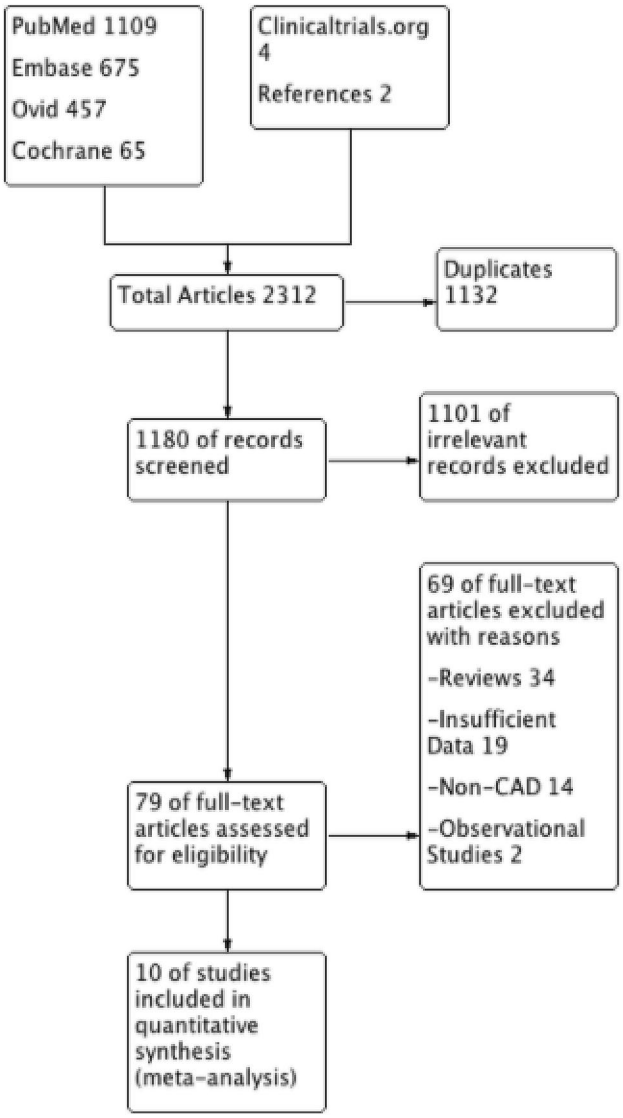

Fig. 1 PRISMA flow diagram showing a trend of the included studies and reasons for exclusions. *CAD* coronary artery disease, *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses

trials selected patients with angiographically proven CAD at least 6 months before randomization. The LoDoCo-2 trial also selected patients with computed tomography angiography (CTA) proven CAD or a coronary artery calcium score greater than 400 Agatston units on coronary artery calcium scanning. The remaining five trials enrolled unstable CAD patients immediately after an ACS event or percutaneous intervention (PCI). The daily dose of colchicine used was mostly 0.5 mg (COLCOT, LoDoCo, and LoDoCo-2) or 1 mg (COLIN and COOL). Tong et al.'s study [10] (COPS) used 0.5 mg twice daily for the first month, followed by 0.5 mg daily for 11 months. Recent RCTs used drug-eluting stents. Deftereos et al. [8] and O'Keefe et al. [13] used a twice-daily dose of 0.5 mg and 0.6 mg of colchicine in patients with

ACS, respectively. The definition of MACE was variable across studies. In the COLCOT, MACE was a composite of ACS, stroke, cardiac arrest, and cardiovascular mortality. The COPS trial described MACE as a sum of ACS, revascularization, stroke, and all-cause death. The LoDoCo trial, however, excluded cardiovascular death from the composite endpoint. All studies excluded patients with active diarrhea, leukopenia, cancer, cardiogenic shock, or end-stage renal disease. The follow-up duration was 12, 22, and 36 months in COPS, COLCOT, and LoDoCo trials, respectively. Detailed characteristics of the included studies are shown in Table S1 and S2 (see the electronic supplementary material), the selection criteria of the included RCTs are given in Table S3, and the trial-level definitions of primary composite endpoints are given in Table S4.

3.1 Pooled Analysis of Efficacy and Safety

At a median follow-up of 1 year, the RR of standard MACE (RR 0.66, 95% CI 0.45–96), ischemic stroke (RR 0.42, 95% CI 0.22–0.81), ACS (RR 0.66, 95% CI 0.45–0.96), and need for revascularization (RR 0.61, 95% CI 0.42–90) were significantly lower in all patients receiving colchicine compared with placebo. However, the overall RRs for cardiac arrest (RR 0.74, 95% CI 0.25–2.15), cardiovascular mortality (RR 0.86, 95% CI 0.57–1.29), and all-cause mortality (RR 1.13, 95% CI 0.87–1.46) were not different between the two groups. The pooled estimate of the trial-defined composite endpoint mirrored the findings of our study-defined MACE. The heterogeneity among the studies comparing the RR of stroke, MACE, ACS, and revascularization was $I^2 = 19\%$, 29%, 38%, and 53%, respectively. There was no heterogeneity in studies comparing cardiac arrest, cardiovascular mortality, and all-cause mortality ($I^2 = 0\%$). All pooled outcomes are given in Fig. 2, the risk of MACE is illustrated in Fig. 3, and the pooled forest plot of trial-defined composite endpoints is given in Figure S1 (see the electronic supplementary material).

Six clinical trials reported on GI adverse events. The overall RR of GI adverse events was significantly higher in the colchicine arm compared with the placebo group (RR 2.10, 95% CI 1.12–3.95). The most common GI adverse events included diarrhea, nausea, and vomiting due to colchicine intolerance. A complete list of GI adverse events is given in Table S5 (see the electronic supplementary material). The heterogeneity among the included studies was $I^2 = 72\%$ (Figure S2).

3.2 Subgroup Analysis

A subgroup analysis based on the type of CAD (stable CAD vs. ACS), doses of colchicine [low dose (0.5 mg) vs. high

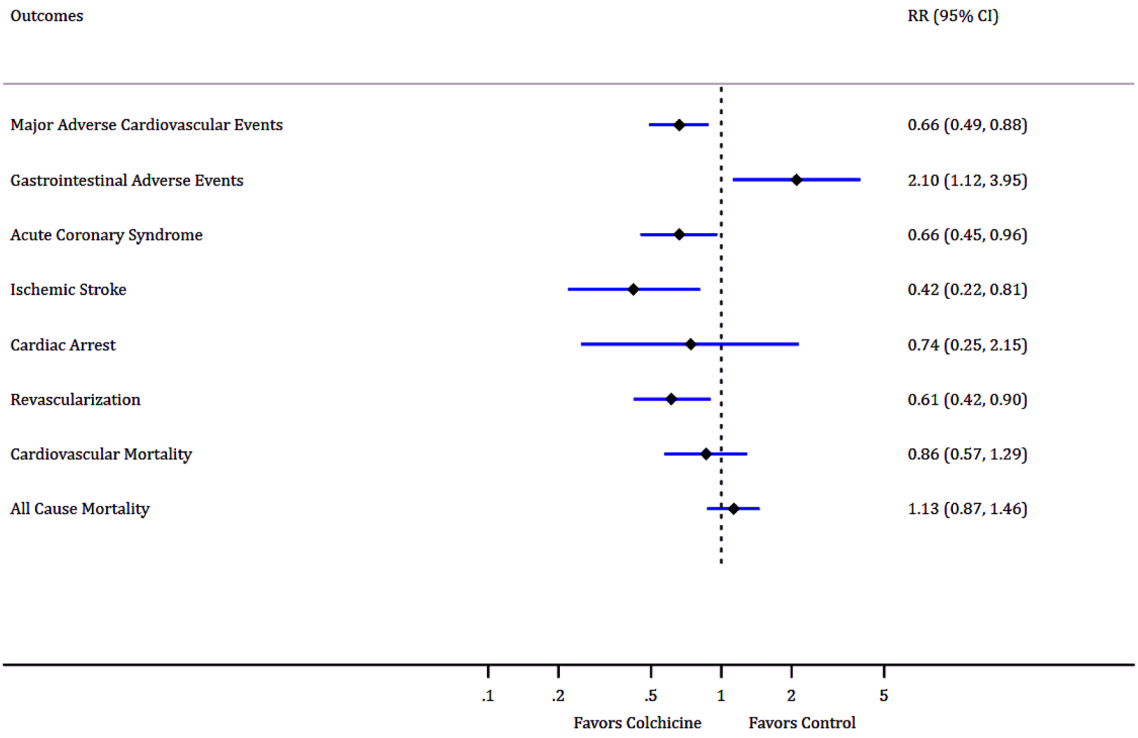

Fig. 2 Forest plot showing pooled outcomes between patients receiving colchicine vs. placebo for all-comers (stable CAD + ACS). *ACS* acute coronary syndrome, *CAD* coronary artery disease

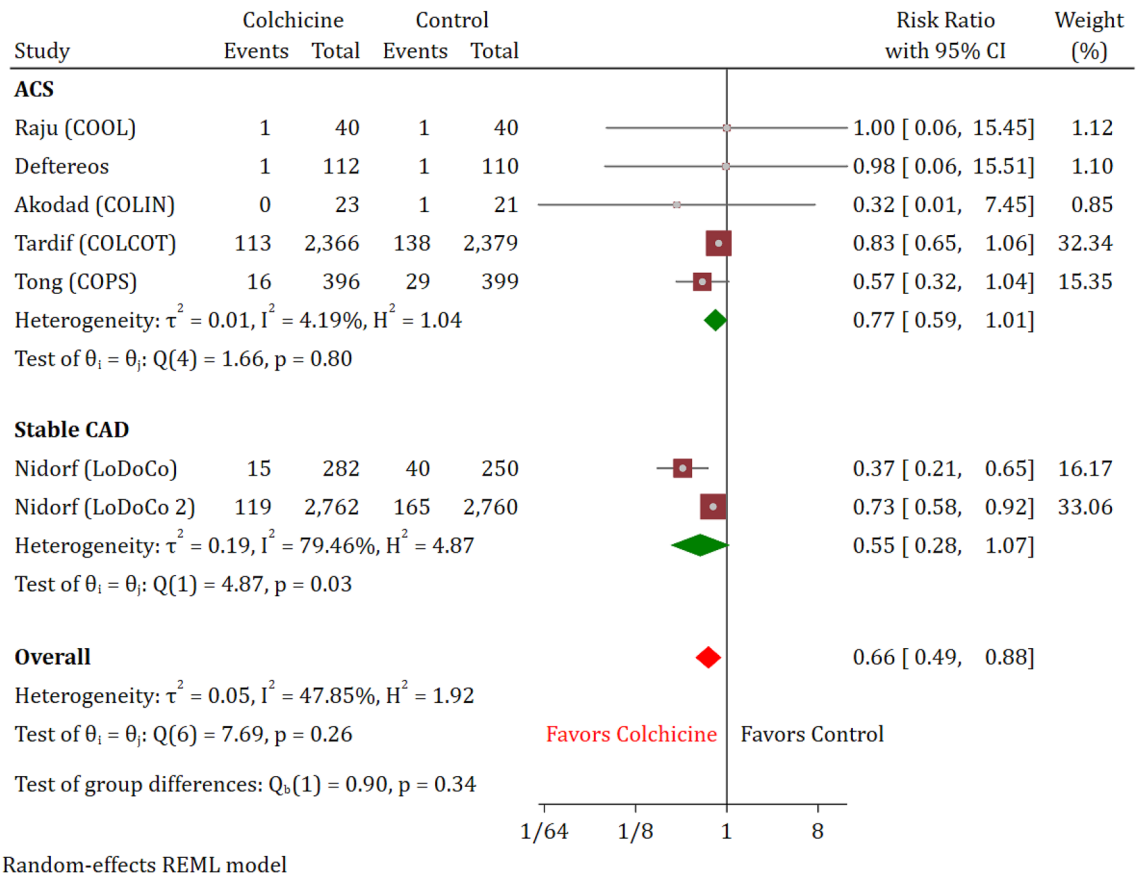

Fig. 3 Pooled and subgroup analysis of MACE by comparing ACS vs. stable CAD patients. *ACS* acute coronary syndrome, *CAD* coronary artery disease, *CI* confidence interval, *MACE* major adverse cardiovascular events

dose (1 mg)] and duration of follow-up (< 6, 12, and > 12 months) was performed. The significantly lower pooled risk of MACE and stroke was driven by studies comparing the ACS population, and there was no significant difference among patients receiving colchicine and placebo for stable CAD. The need for revascularization was lower with colchicine in both stable CAD (RR 0.76, 95% CI 0.61–0.96) and ACS patients (RR 0.49, 95% CI 0.32–0.75). There remained no significant difference in the incidence of cardiac arrest, cardiovascular mortality, and all-cause mortality between the two arms in both stable CAD and ACS populations. Contrary to the pooled analysis, there was no significant difference in the risk of ACS between patients receiving colchicine and those in the control arm in stable CAD and ACS patients (Figures S3–S8; see the electronic supplementary material). Only patients on a low dose (0.5 mg) of colchicine showed a significantly lower incidence of MACE (RR 0.66, 95% CI 0.48–0.89), revascularization (RR 0.62, 95% CI 0.43–0.91), and stroke (RR 0.43, 95% CI 0.23–0.81) in the colchicine group compared with placebo. A stratified analysis of a patient population receiving a 1-mg dose of colchicine (COOL, Colchicine-PCI, and COLIN) showed no significant difference in the risk of MACE, MI, and stroke between the colchicine and placebo groups. Similarly, the dose of colchicine had no impact on the risk of cardiac arrest, cardiovascular mortality, and all-cause mortality (Figures S9–S15). Another subgroup analysis showed that MACE (RR 0.65, 95% CI 0.43–0.99) and stroke (RR 0.43, 95% CI 0.19–0.96) were significantly lower with colchicine only in studies with a follow-up duration of > 12 months. The incidence of cardiac arrest, cardiovascular mortality, and all-cause mortality remained invariantly similar in the two groups at all follow-up durations (Figures S16–S21).

3.3 Sensitivity Analysis

The sensitivity analysis mostly showed no influence of any individual trial except that omitting the COLCOT showed a significantly lower incidence of ACS with colchicine (RR 0.54, 95% CI 0.31–0.93). Similarly, the significantly lower risk of MACE with colchicine was attenuated with the exclusion of LoDoCo-2 and COPS trials from pooled estimates

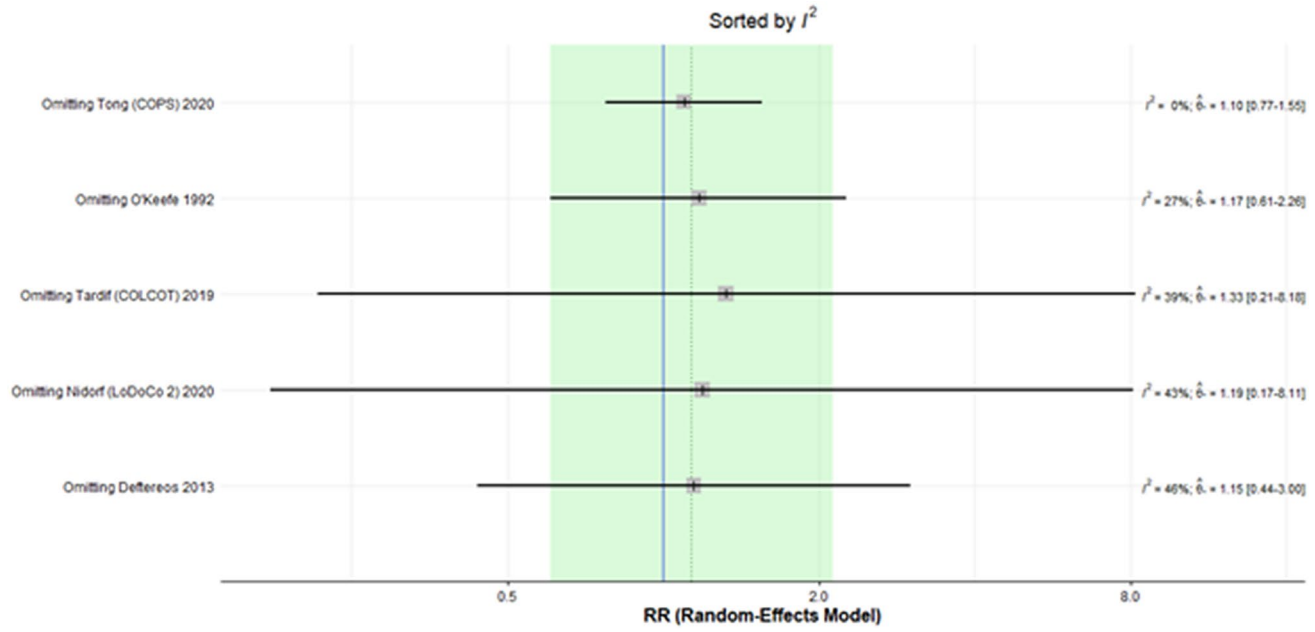

Fig. 4 Sensitivity analysis by leave-one-out method for all-cause mortality. *RR* risk ratio

(Figures S22–S24; see the electronic supplementary material). There was no impact of any single study on all-cause mortality (Fig. 4).

3.4 Methodological and Publication Bias

Two independent reviewers (SN and SZ) assessed bias in the included studies. Any conflict was resolved by mutual discussion with WU. The overall quality of the included studies was high. Two of the included RCTs were open-label, posing some risk of selection bias due to the absence of allocation concealment. The risk of performance, detection, and reporting bias was low as hard clinical outcomes were assessed and reported adequately by the included trials. Due to appropriate randomization across all studies, the risk of confounding in RCTs was minimal. The individual study and overall bias summaries are reported in Fig. 5. The better quality of RCTs was confirmed on the Oxford Jadad scoring criteria showing an overall score of > 3 (Table S6; see the electronic supplementary material). On visual assessment, our funnel plot for MACE showed a symmetrical distribution of studies, demonstrating minimal publication bias. The smaller studies were plotted at the bottom, and the studies with the greater effect size were closer to the vertical axis. The limited scatter on the graph was due to sampling variation and not due to publication bias (Fig. 6).

4 Discussion

The present meta-analysis represents the largest amount of evidence on the safety and efficacy of colchicine in patients with stable CAD or ACS. Our results suggest that in patients with stable CAD and ACS, colchicine might lower the risk of MACE, ACS, the need for revascularization, and ischemic stroke by 29%, 34%, 39%, and 58%, respectively. However, a stratified analysis based on the type of CAD (stable CAD and ACS), the dose of colchicine used, and follow-up duration showed significant variations. The lower incidence of MACE and stroke was only present at long-duration follow-ups (> 12 months) and in those receiving low-dose colchicine (0.5 mg) after ACS. While colchicine significantly reduced the incidence of the need for revascularization in both ACS and stable CAD, it offered no benefits in terms of reducing the incidence of MACE, stroke, and ACS in patients with stable CAD. Overall, the non-beneficial effects of colchicine in terms of reducing cardiac arrest, cardiovascular mortality, and all-cause mortality were invariant across the stratified analysis of low-dose (0.5 mg daily) and high-dose colchicine (1 mg daily) and in patients with stable CAD and ACS. The net risk of GI adverse events was increased by twofold in patients receiving colchicine; however, these were mostly limited to nausea, vomiting, and diarrhea.

Fig. 5 Detailed methodological quality assessment of the included studies. All studies are checked for 5 different types of biases, and the green plus sign indicates lower risk, blank indicates an unknown risk, and a red negative sign indicates a higher risk of the corresponding bias.

To date, ten clinical trials have evaluated the utility of colchicine in conjunction with standard secondary prevention therapy of CAD [6, 8–16]. O'Keefe et al. were the first to compare the role of colchicine in patients with ACS undergoing angioplasty [13]. At a median follow-up of 5.5 months, there was no significant benefit observed with respect to lower lesion restenosis in the colchicine arm. However, the clinical relevance of restenosis after coronary angioplasty is uncertain, the trial was vastly underpowered (197 patients), and it had unequal randomization in the experimental and control arms (2:1, respectively). Consequently, it did not gain much clinical traction [13]. After limited clinical research for 2 decades, interest in colchicine therapy was rekindled with the COOL trial by Raju et al. [14]. This study primarily investigated the effect of colchicine on platelet function tests and a high sensitivity inflammatory marker [C-reactive protein (CRP)]; however, this study also failed to provide evidence of a lower inflammation rate or rate of ACS events in patients on colchicine [14].

Although from a pathophysiological standpoint the platelet activity and titers of inflammatory biomarkers can provide plausible evidence of an impending ACS event, the

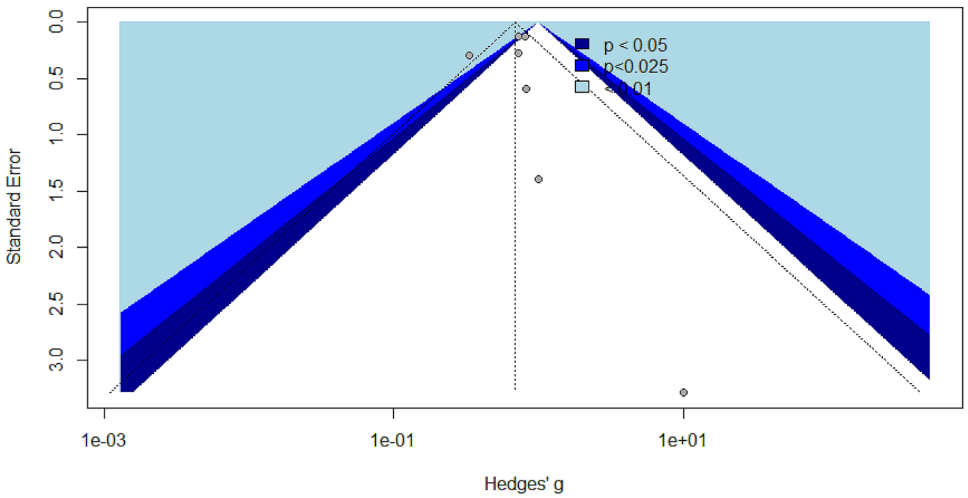

Fig. 6 Funnel plot for MACE demonstrating the symmetrical distribution of studies and hence no publication bias. The vertical axis of the plot used the standard error to estimate the sample size of the studies, plotting large population studies on top and smaller at the bottom. The horizontal spread reflects the power and effect size of the included studies. *MACE* major adverse cardiovascular events

reliability of the findings is uncertain given the variability of platelet function tests due to administered antiplatelet therapy. Deftereos et al. also conducted a study to determine the role of colchicine in the prevention of in-stent restenosis [8]. The study suggested that by significantly lowering the rate of restenosis, colchicine also reduced the risk of mortality and the need for revascularization. The study design was remarkable for not being driven by the clinical events; rather, all patients underwent diagnostic coronary angiography to look for anatomic restenosis [8]. In the context of recent literature, the generalizability of these findings is uncertain, as an assumption of functional relevance based merely on the angiographic appearance of restenosis in the absence of clinical symptoms could be misleading [17]. The external validity of this study is also limited, given the constraints of a diabetic-only population receiving only BMS [8]. Of the included studies, the COLIN trial included 44 patients, duplicating the methodology of the COOL trials. Again, colchicine use was not associated with either a reduction in inflammatory markers (CRP) or a lowering of the rate of MACE and its components [6]. A major limitation of this study, apart from being an open-label, non-placebo-controlled trial, was that the primary outcomes measured were surrogate inflammatory markers rather than hard clinical outcomes [6]. Most trials were underpowered due to their small sample sizes and had a high amount of heterogeneity in the inclusion criteria and outcome assessors. The follow-up duration ranged from 1 to a maximum of 6 months; hence, the long-term effects of colchicine could not be assessed.

The LoDoCo trial was the first to compare the long-term effects of colchicine, in 532 patients with stable CAD [11]. The study demonstrated a significantly lower incidence of the primary composite event (MACE) (by 67%, $p \leq 0.001$) with colchicine compared to placebo at 3 years [11]. The pooled results were entirely driven by the lower risk of ACS events (4.6% vs. 13%), with no significant difference in other components of MACE (out-of-hospital cardiac arrest and stroke) [11]. This trial was conducted on a prospective, randomized, observer-blinded endpoint (PROBE) protocol, where the included population was not blinded to the treatment arm [11]. This, along with the lack of a placebo arm, poses a theoretical risk of selection and reporting biases [11]. By contrast, the recently published LoDoCo-2 trial was a randomized-control, double-blinded study, which was adequately powered, recruiting 5522 patients with CAD [12]. The results of this study were in line with the previous study, where a 31% lower incidence of MACE in the colchicine arm was entirely driven by the lower rate of ACS [12]. Overall, this trial demonstrated that colchicine is safe in patients with chronic CAD. Interestingly, this trial's population was only 14–16% female, and the inflammatory markers and lipid panel for the comparison groups were not measured. Contrary to the individual trials, our pooled analysis showed no benefits with colchicine in patients with stable CAD in terms of lowering ACS or other ischemic endpoints.

The recently published COLCOT and COPS trials hurdled some of the design limitations of prior studies by including a well-balanced randomized population with a recent ACS event [2]. The COLCOT demonstrated a significantly lower incidence of MACE in patients on colchicine, while the risk of MACE was not statistically different between the two groups in the COPS trial. Overall, the beneficial effects of colchicine in terms of a lower incidence of MACE in the COLCOT should be taken with similar caveats as LoDoCo. The pooled outcomes were largely explained by the nearly four times greater rate of stroke and a two times higher risk of angina in the placebo arm. The colchicine group was not found to be superior to placebo in terms of MI, mortality, or cardiac arrest in the breakdown of the primary endpoint [2, 7]. Interestingly, the components of MACE in the COPS trial did not include angina, but it

showed a non-significantly different risk of stroke between the two arms. Contrary to the COLCOT, the COPS trial demonstrated a higher risk of mortality and a lower rate of revascularization with colchicine. Our sensitivity analysis showed no influence of any individual trial on pooled mortality estimates; however, there was a significant influence of the COLCOT on net ACS and the COPS trial on MACE.

Although all these contemporary clinical trials (LoDoCo, LoDoCo-2, COLCOT, and COPS) were primarily event driven, patient recruitment criteria and outcomes were conflicting [9–12]. The LoDoCo trials enrolled stable CAD patients 6 months after an index MI event, while the COLCOT and COPS trials included unstable CAD patients within 1 month of ACS. Similarly, the proportion of female patients, the proportion of patients with previous coronary artery bypass grafting (CABG), and the components of MACE in these trials were variable [9–12]. While five previous meta-analyses attempted to bring consensus on the use of colchicine use in patients with CAD, most of these were published before the release of the newer larger-scale RCTs. Previous studies failed to calculate adjusted MACE, and most of the important subgroup and sensitivity analyses were missing [18–21]. Our study adds to the existing literature by providing updated meta-analysis; our findings deviate from the findings of a prior meta-analysis by Ullah et al. [22], Aimo et al. and review by Kurup et al. due to the addition of large-scale contemporary trials [19, 20]. We believe that in light of this recent evidence, the applicability of the previous meta-analysis and individual RCT is limited. Results from the ongoing CLEAR-SYNERGY clinical trial evaluating colchicine and spironolactone in patients with STEMI might shed more light on the merits of colchicine. The detailed characteristics of the prior meta-analyses are given in Table S7 (see the electronic supplementary material).

4.1 Limitations

Our study is constrained by the limitations of the included data. Due to the paucity of data and lack of patient-level data, we were unable to calculate the adjusted RR based on baseline comorbidities. Although the inherent heterogeneity in the selection criteria of studies, such as variable doses of colchicine (0.5 mg vs. 1 mg) and non-identical patient populations in the LoDoCo trials (stable CAD) and the COLCOT and the COPS trial (early post-MI), were accounted for in the subgroup analysis, the impact of unmeasured potential confounders could not be excluded. Given the heterogeneity in the follow-up durations and methodologies of the included studies, our results should be interpreted with caution and in light of their limitations. Of the included trials, the COPS trial was the only trial showing increased mortality with colchicine; however, it did not affect our pooled estimate on sensitivity analysis. Ongoing clinical trials are recruiting patients with new-generation stents using novel secondary preventive therapies. These studies will further clarify the impact of stent design and medication use on the overall benefits of colchicine.

5 Conclusion

In patients with ACS, low-dose colchicine in conjunction with standard secondary prevention therapy might reduce the incidence of MACE, stroke, and the need for revascularization at long follow-up durations. Colchicine might offer no benefits in reducing the risk of ischemic events in patients with stable angina. More studies are needed to validate our findings.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40256-021-00485-7.

Declarations

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Conflict of interest Waqas Ullah, Shujaul Haq, Salman Zahid, Smitha Narayana Gowda, Patrick Ottman, Sameer Saleem, Ihab Hamzeh, Salim S. Virani, Mahboob Alam, and David L. Fischman declare that they have no potential conflicts of interest that might be relevant to the contents of this article.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Authors' contributions WU: Conceptualization, analysis, and writing. SZ: Revision and quality assessment of articles. SH: Writing manuscript. SNG: Data collection and quality assessment. PO: Data collection. SS: Writing. IH: Critical review. SV: Critical review and editing. MA: Editing. DF: Supervision and critical review.

References

1. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med. 2005;352(16):1685–95. https://doi.org/10.1056/NEJMra043430.
2. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002;105(9):1135–43. https://doi.org/10.1161/hc0902.104353.

3. Libby P, Ridker PM, Hansson GK, Leducq Transatlantic Network on Atherothrombosis. Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol. 2009;54(23):2129–38. https://doi.org/10.1016/j.jacc.2009.09.009.
4. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ, CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377(12):1119–31. https://doi.org/10.1056/NEJMoa1707914.
5. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, Mam V, Hasan A, Rosenberg Y, Iturriaga E, Gupta M, Tsigoulis M, Verma S, Clearfield M, Libby P, Goldhaber SZ, Seagle R, Ofori C, Saklayen M, Butman S, Singh N, Le May M, Bertrand O, Johnston J, Paynter NP, Glynn RJ, CIRT Investigators. Low-dose methotrexate for the prevention of atherosclerotic events. N Engl J Med. 2019;380(8):752–62. https://doi.org/10.1056/NEJMoa1809798.
6. Akodad M, Lattuca B, Nagot N, Georgescu V, Buisson M, Cristol JP, Leclercq F, Macia JC, Gervasoni R, Cung TT, Cade S, Cransac F, Labour J, Dupuy AM, Roubille F. COLIN trial: value of colchicine in the treatment of patients with acute myocardial infarction and inflammatory response. Arch Cardiovasc Dis. 2017;110(6–7):395–402. https://doi.org/10.1016/j.acvd.2016.10.004.
7. Dalbeth N, Lauterio TJ, Wolfe HR. Mechanism of action of colchicine in the treatment of gout. Clin Ther. 2014;36(10):1465–79. https://doi.org/10.1016/j.clinthera.2014.07.017.
8. Deftereos S, Giannopoulos G, Raisakis K, Kossyvakis C, Kaoukis A, Panagopoulou V, Driva M, Hahalis G, Pyrgakis V, Alexopoulos D, Manolis AS, Stefanadis C, Cleman MW. Colchicine treatment for the prevention of bare-metal stent restenosis in diabetic patients. J Am Coll Cardiol. 2013;61(16):1679–85. https://doi.org/10.1016/j.jacc.2013.01.055.
9. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, Berry C, López-Sendón J, Ostadal P, Koenig W, Angoulvant D, Grégoire JC, Lavoie MA, Dubé MP, Rhainds D, Provencher M, Blondeau L, Orfanos A, L'Allier PL, Guertin MC, Roubille F. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med. 2019;381(26):2497–505. https://doi.org/10.1056/NEJMoa1912388.
10. Tong DC, Quinn S, Nasis A, Hiew C, Roberts-Thomson P, Adams H, Sriamareswaran R, Htun NM, Wilson W, Stub D, van Gaal W, Howes L, Collins N, Yong A, Bhindi R, Whitbourn R, Lee A, Hengel C, Asrress K, Freeman M, Amerena J, Wilson A, Layland J. Colchicine in patients with acute coronary syndrome: the Australian COPS randomized clinical trial. Circulation. 2020;142(20):1890–900. https://doi.org/10.1161/CIRCULATIONAHA.120.050771.
11. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. J Am Coll Cardiol. 2013;61(4):404–10. https://doi.org/10.1016/j.jacc.2012.10.027.
12. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, The SHK, Xu XF, Ireland MA, Lenderink T, Latchem D, Hoogslag P, Jerzewski A, Nierop P, Whelan A, Hendriks R, Swart H, Schaap J, Kuijper AFM, van Hessen MWJ, Saklani P, Tan I, Thompson AG, Morton A, Judkins C, Bax WA, Dirksen M, Alings M, Hankey GJ, Budgeon CA, Tijssen JGP, Cornel JH, Thompson PL, LoDoCo2 Trial Investigators. Colchicine in patients with chronic coronary disease. N Engl J Med. 2020;383(19):1838–47. https://doi.org/10.1056/NEJMoa2021372.
13. O'Keefe JH Jr, McCallister BD, Bateman TM, Kuhnlein DL, Ligon RW, Hartzler GO. Ineffectiveness of colchicine for the prevention of restenosis after coronary angioplasty. J Am Coll Cardiol. 1992;19(7):1597–600. https://doi.org/10.1016/0735-1097(92)90624-v.
14. Raju NC, Yi Q, Nidorf M, Fagel ND, Hiralal R, Eikelboom JW. Effect of colchicine compared with placebo on high sensitivity C-reactive protein in patients with acute coronary syndrome or acute stroke: a pilot randomized controlled trial. J Thromb Thrombolysis. 2012;33(1):88–94. https://doi.org/10.1007/s11239-011-0637-y.
15. Hennessy T, Soh L, Bowman M, Kurup R, Schultz C, Patel S, Hillis GS. The low dose colchicine after myocardial infarction (LoDoCo-MI) study: a pilot randomized placebo controlled trial of colchicine following acute myocardial infarction. Am Heart J. 2019;215:62–9. https://doi.org/10.1016/j.ahj.2019.06.003.
16. Shah B, Pillinger M, Zhong H, Cronstein B, Xia Y, Lorin JD, Smilowitz NR, Feit F, Ratnapala N, Keller NM, Katz SD. Effects of acute colchicine administration prior to percutaneous coronary intervention: COLCHICINE-PCI randomized trial. Circ Cardiovasc Interv. 2020;13(4):e008717. https://doi.org/10.1161/CIRCINTERVENTIONS.119.008717
17. Ullah W, Roomi S, Abdullah HM, Mukhtar M, Ali Z, Ye P, Haas DC, Figueredo VM. Diagnostic accuracy of cardiac magnetic resonance versus fractional flow reserve: a systematic review and meta-analysis. Cardiol Res. 2020;11(3):145–54. https://doi.org/10.14740/cr1028.
18. Hemkens LG, Ewald H, Gloy VL, Arpagaus A, Olu KK, Nidorf M, Glinz D, Nordmann AJ, Briel M. Cardiovascular effects and safety of long-term colchicine treatment: cochrane review and meta-analysis. Heart. 2016;102(8):590–6. https://doi.org/10.1136/heartjnl-2015-308542.
19. Aimo A, Pascual Figal DA, Bayes-Genis A, Emdin M, Georgiopoulos G. Effect of low-dose colchicine in acute and chronic coronary syndromes: a systematic review and meta-analysis. Eur J Clin Investig. 2021;51(4):e13464. https://doi.org/10.1111/eci.13464.
20. Kurup R, Galougahi KK, Figtree G, Misra A, Patel S. The role of colchicine in atherosclerotic cardiovascular disease. Heart Lung Circ. 2021. https://doi.org/10.1016/j.hlc.2020.11.010.
21. Samuel M, Tardif JC, Bouabdallaoui N, Khairy P, Dubé MP, Blondeau L, Guertin MC. Colchicine for secondary prevention of cardiovascular disease: a systematic review and meta-analysis of randomized controlled trials. Can J Cardiol. 2020. https://doi.org/10.1016/j.cjca.2020.10.006.
22. Ullah W, Gowda SN, Fischman D. Safety and efficacy of colchicine in patients with coronary artery disease: a systematic review and meta-analysis. Cardiovasc Revascularization Med. 2021;23:1–6. https://doi.org/10.1016/j.carrev.2020.06.004